

What Is Claimed Is:

1. A method for preparing microparticles, comprising:
preparing an emulsion comprising an aqueous peptide solution and a biodegradable, biocompatible polymer dissolved in a halogenated solvent;
combining the emulsion with a coacervating agent that is free from solvents for the polymer to form a combined phase;
extracting the halogenated solvent from the combined phase with an extraction medium that is a non-solvent for the polymer and a solvent for the halogenated solvent and the coacervating agent, whereby microparticles precipitate out of the extraction medium; and
washing the precipitated microparticles in a non-aqueous washing system that is either (1) 100% ethanol or (2) a blend of ethanol and heptane to thereby reduce a level of residual halogenated solvent.
2. The method of claim 1, wherein the peptide is a luteinizing-hormone-releasing hormone (LHRH) analogue.
3. The method of claim 2, wherein the halogenated solvent is methylene chloride.
4. The method of claim 1, wherein the blend is a 3:1 ratio of ethanol to heptane.
5. The method of claim 1, wherein the blend is a 1:1 ratio of ethanol to heptane.
6. The method of claim 1, wherein a temperature of the washing system is between about 10° and about 26° C.
7. The method of claim 3, wherein the coacervating agent is silicone oil.
8. The method of claim 1, wherein the halogenated solvent is methylene chloride.
9. The method of claim 1, wherein the coacervating agent is silicone oil.
10. The method of claim 7, wherein the extraction medium is heptane.
11. The method of claim 1, wherein the extraction medium is heptane.

12. The method of claim 1, wherein the biodegradable, biocompatible polymer is selected from the group consisting of poly(glycolic acid), poly(d,l-lactic acid), poly(l-lactic acid), and copolymers of the foregoing.
13. The method of claim 3, wherein the biodegradable, biocompatible polymer is selected from the group consisting of poly(glycolic acid), poly(d,l-lactic acid), poly(l-lactic acid), and copolymers of the foregoing.
14. The method of claim 1, wherein the washing step is carried out until the level of residual halogenated solvent in the washed microparticles is less than about 0.06% by weight.
15. The method of claim 3, wherein the washing step is carried out until the level of residual halogenated solvent in the washed microparticles is less than about 0.06% by weight.
16. The method of claim 1, further comprising after said extracting step: drying the precipitated microparticles.
17. The method of claim 3, further comprising after said extracting step: drying the precipitated microparticles.
18. The method of ~~claim 1~~, further comprising after said washing step: final drying the washed microparticles.
19. The method of claim 16, further comprising after said washing step: final drying the washed microparticles.
20. A method for preparing microparticles, comprising:
contacting microparticles comprising a biodegradable, biocompatible polymer matrix comprising a peptide and a halogenated solvent with a non-aqueous washing system to thereby reduce a level of residual halogenated solvent in the microparticles, wherein the washing system is either (1) 100% ethanol or (2) a blend of ethanol and heptane; and
recovering the microparticles from the washing system.
21. The method of claim 20, wherein the peptide is a luteinizing-hormone-releasing hormone (LHRH) analogue.
22. The method of claim 21, wherein the halogenated solvent is methylene chloride.

23. The method of claim 20, wherein the blend is a 3:1 ratio of ethanol to heptane.
24. The method of claim 20, wherein the blend is a 1:1 ratio of ethanol to heptane.
25. The method of claim 20, wherein a temperature of the washing system is between about 10° and 26° C.
26. The method of claim 20, wherein the contacting step is carried out until the level of residual halogenated solvent in the recovered microparticles is less than about 0.06% by weight.
27. Microparticles prepared by the method of claim 1.
28. The microparticles of claim 27, wherein the peptide is a luteinizing-hormone-releasing hormone (LHRH) analogue.
29. A method for preparing microparticles, comprising:
contacting microparticles comprising a biodegradable, biocompatible polymer matrix comprising goserelin and a halogenated solvent with a non-aqueous washing system to thereby reduce a level of residual halogenated solvent to less than about 0.06% by weight of the microparticles, wherein the washing system is either (1) 100% ethanol or (2) a blend of ethanol and heptane; and
recovering the microparticles from the washing system.
30. A method for preparing microparticles, comprising:
preparing a first phase comprising a biodegradable, biocompatible polymer and a halogenated solvent;
preparing an aqueous second phase comprising a peptide;
combining the first phase and the second phase under the influence of a mixer to form an emulsion;
combining the emulsion with a coacervating agent that is free from solvents for the polymer to form a combined phase;
extracting the halogenated solvent from the combined phase with an extraction medium that is a non-solvent for the polymer and a solvent for the halogenated solvent and the coacervating agent, whereby microparticles precipitate out of the extraction medium; and

washing the precipitated microparticles in a non-aqueous washing system that is either (1) 100% ethanol or (2) a blend of ethanol and heptane to thereby reduce a level of residual halogenated solvent.

31. The method of claim 30, wherein the mixer is a static mixer.
32. The method of claim 30, wherein the peptide is a luteinizing-hormone-releasing hormone analogue.
33. The method of ~~claim 32~~, wherein the halogenated solvent is methylene chloride.
34. The method of claim 30, wherein the blend is a 3:1 ratio of ethanol to heptane.
35. The method of claim 30, wherein the blend is a 1:1 ratio of ethanol to heptane.
36. The method of claim 30, wherein a temperature of the washing system is between about 10° and about 26° C.
37. The method of claim 33, wherein the coacervating agent is silicone oil.
38. The method of claim 30, wherein the halogenated solvent is methylene chloride.
39. The method of claim 30, wherein the coacervating agent is silicone oil.
40. The method of claim 37, wherein the extraction medium is heptane.
41. The method of claim 30, wherein the extraction medium is heptane.
42. The method of claim 30, wherein the biodegradable, biocompatible polymer is selected from the group consisting of poly(glycolic acid), poly(d,l-lactic acid), poly(l-lactic acid), and copolymers of the foregoing.
43. The method of claim 33, wherein the biodegradable, biocompatible polymer is selected from the group consisting of poly(glycolic acid), poly(d,l-lactic acid), poly(l-lactic acid), and copolymers of the foregoing.
44. The method of claim 30, wherein the washing step is carried out until the level of residual halogenated solvent in the washed microparticles is less than about 0.06% by weight.

45. The method of claim 33, wherein the washing step is carried out until the level of residual halogenated solvent in the washed microparticles is less than about 0.06% by weight.
46. The method of claim 2, wherein the LHRH analogue is goserelin.
47. The method of claim 21, wherein the LHRH analogue is goserelin.
48. The method of claim 32, wherein the LHRH analogue is goserelin.
49. A method for preparing microparticles, comprising:
preparing an emulsion comprising an aqueous peptide solution and a biodegradable, biocompatible polymer dissolved in a halogenated solvent;
combining the emulsion with a coacervating agent that is free from solvents for the polymer to form a combined phase;
extracting the halogenated solvent from the combined phase with an extraction medium that is a non-solvent for the polymer and a solvent for the halogenated solvent and the coacervating agent, whereby microparticles precipitate out of the extraction medium; and
washing the precipitated microparticles in a non-aqueous washing system that comprises ethanol.
50. A method for preparing microparticles, comprising:
contacting microparticles comprising a biodegradable, biocompatible polymer matrix containing an active agent and an organic solvent with a non-aqueous washing system to thereby reduce a level of residual organic solvent in the microparticles, wherein the non-aqueous washing system is either (1) 100% ethanol or (2) a blend of ethanol and heptane; and
recovering the microparticles from the non-aqueous washing system.
51. The method of claim 50, wherein the active agent is selected from the group consisting of risperidone, 9-hydroxyrisperidone, and pharmaceutically acceptable salts thereof.
52. The method of claim 50, wherein the active agent is a peptide.
53. The method of claim 51, wherein the organic solvent is a solvent blend comprising ethyl acetate and benzyl alcohol.

54. The method of claim 52, wherein the non-aqueous washing system is 100% ethanol.
55. The method of claim 50, further comprising prior to said contacting step:
preparing an emulsion that comprises the active agent, the biodegradable, biocompatible polymer, and the organic solvent; and
extracting the organic solvent from the emulsion using an extraction liquid to thereby form microparticles containing the active agent.
56. The method of claim 50, further comprising prior to said contacting step:
preparing a first phase that comprises the active agent, the biodegradable, biocompatible polymer, and the organic solvent, wherein the organic solvent is a solvent for the biodegradable, biocompatible polymer;
preparing a second phase that is free from solvents for the biodegradable, biocompatible polymer;
combining the first phase and the second phase to form an emulsion;
extracting the organic solvent from the emulsion using an extraction medium, whereby microparticles precipitate out of the extraction medium.
57. The method of claim 56, wherein the extraction medium is a non-solvent for the biodegradable, biocompatible polymer and a solvent for the organic solvent.
58. The method of claim 52, wherein the peptide is goserelin.
59. The method of claim 56, wherein the second phase comprises silicone oil.
60. A method for preparing microparticles, comprising:
preparing a first phase, the first phase comprising an active agent, a biodegradable, biocompatible polymer, and a solvent;
preparing a second phase, wherein the first phase is substantially immiscible with the second phase;
combining the first phase and the second phase to form an emulsion;
extracting solvent from the emulsion using an extraction liquid to thereby form microparticles containing the active agent; and

washing the microparticles with a non-aqueous washing system to thereby reduce the level of residual solvent in the microparticles, wherein the non-aqueous washing system comprises ethanol.

61. The method of claim 60, wherein the active agent is selected from the group consisting of risperidone, 9-hydroxyrisperidone, and pharmaceutically acceptable salts thereof.

62. The method of claim 61, wherein the solvent is a solvent blend comprising ethyl acetate and benzyl alcohol.

63. A method for preparing microparticles, comprising:

preparing an emulsion comprising an aqueous peptide solution and a biodegradable, biocompatible polymer dissolved in a solvent;

combining the emulsion with a coacervating agent that is free from solvents for the polymer to form a combined phase;

extracting solvent from the combined phase in an extraction medium that is a non-solvent for the polymer and a solvent for the solvent and the coacervating agent, whereby microparticles precipitate out of the extraction medium; and

washing the precipitated microparticles in 100% ethanol.

64. The method of claim 63, wherein the peptide is goserelin.

65. The method of claim 63, wherein the coacervating agent is silicone oil.

66. The method of claim 63, wherein the extraction medium is heptane.

67. The method of claim 63, wherein the washing step is carried out until the level of solvent in the microparticles is less than about 0.06% by weight.

68. The method of claim 60, wherein the non-aqueous washing system is 100% ethanol.

69. The method of claim 50, wherein the contacting step is carried out until the level of residual organic solvent is less than about 0.2% by weight.

70. The method of claim 53, wherein the contacting step is carried out until the level of ethyl acetate is less than about 0.2% by weight and the level of benzyl alcohol is less than about 0.2% by weight.

71. A method for preparing microparticles, comprising:

contacting microparticles comprising a biodegradable, biocompatible polymer matrix containing an active agent and an organic solvent with a non-aqueous washing system to thereby reduce a level of residual organic solvent in the microparticles, wherein the non-aqueous washing system is either (1) 100% alcohol or (2) a blend of alcohol and a liquid alkane; and

recovering the microparticles from the non-aqueous washing system.

72. The method of claim 71, wherein the active agent is a peptide.

73. The method of claim 72, wherein the non-aqueous washing system is the blend of alcohol and a liquid alkane.

74. A method for preparing microparticles, comprising:

preparing an emulsion comprising an active agent and a biodegradable, biocompatible polymer dissolved in a solvent;

combining the emulsion with a coacervating agent that is free from solvents for the polymer to form a combined phase; and

extracting the solvent from the combined phase with a solvent blend of a hardening solvent and a washing solvent, to thereby form hardened microparticles.

75. The method of claim 74, further comprising after the extracting step:
rinsing the microparticles with the hardening solvent.

76. The method of claim 74, wherein the hardening solvent is a liquid alkane.

77. The method of claim 74, wherein the washing solvent is an alcohol.

78. The method of claim 76, wherein the washing solvent is an alcohol.

79. The method of claim 74, wherein the hardening solvent is selected from the group consisting of heptane, hexane, cyclohexane, diethyl ether, petroleum ether, mineral oil, fatty acid esters, and caprylate triglyceride.

80. The method of claim 74, wherein the washing solvent is selected from the group consisting of ethanol and isopropanol.

81. The method of claim 74, wherein the hardening solvent is heptane and the washing solvent is ethanol.

82. The method of claim 74, wherein the solvent is a halogenated solvent.

83. The method of claim 74, wherein the coacervating agent is silicone oil.

84. The method of claim 75, wherein the hardening solvent is heptane.

85. The method of claim 81, further comprising after the extracting step:
rinsing the microparticles with heptane.

86. The method of claim 74, further comprising after the extracting step:
rinsing the microparticles with a second hardening solvent different from the
hardening solvent.

87. Microparticles prepared by the method of claim 74.